PATENT SPECIFICATION

1,062,357

NO DRAWINGS

1,062,357

Date of Application and filing Complete Specification: July 29, 1965.

No. 32543/65.

Application made in United States of America (No. 442,205) on March 23, 1965.

Complete Specification Published: March 22, 1967.

Index at acceptance:—C2 C(1E6K4, 1E6K6, 1E6K7, 1E7E1, 1E7F1, 1E7H1, 1E7H2, 1E7L, 1E7N5, 1E7P3, 1F2A2, 1F2C4, 1F2C5, 1F2C6, 1F2D3, 1K2A1, 1K2B, 1K2C3, 1Q2, 1Q4, 1Q6C, 1Q7A, 1Q8A, 1Q8B, 1Q8C, 1Q9B, 1Q9C, 1Q9F1, 1Q9F2, 1Q11D, 1Q11G, 1Q11J, 2B4A4, 2B4F, 2B4G1, 2B4G4, 2B9, 2D19, 3A12A4A, 3A12A4C, 3A12B1, 3A12B2, 3A12C1, 3A12C6, 3A14A3A, 3A14A5, 3A14A8D, 3C5A4, 3C5B, 3C5C4, 3C5C7, 3C5E2)

Int. Cl.:—C 07 d 51/34, C 07 d 57/00, C 07 d 99/02

COMPLETE SPECIFICATION

Quinazolone Derivatives

ERRATUM

SPECIFICATION No. 1,062,357

Page 11, line 18, *after* "the" *insert* "corresponding 2-halo-3,4-dihydroquinazoline-"

THE PATENT OFFICE
10th June 1969

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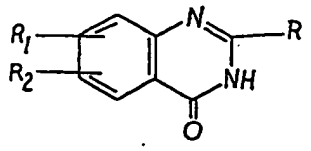

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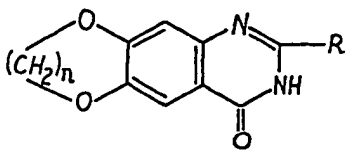

wherein R_1 and R_2 are each hydrogen, fluorine, chlorine, bromine, trifluoromethyl, lower alkyl, lower alkoxy or lower alkylthio, containing from one to four carbon atoms, with at

[*Price 4s. 6d.*]

the alkyl and alkenyl groups in R containing up to five carbon atoms in each case as previously indicated. Other preferred compounds include those where n is one and R is amino. Typical of the specific members of this series are such compounds as 2 - (N,N - dimethylamino) - 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one, 2 - (N,N - diethylamino) 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one, 2 - (N,N - diallylamino) - 6,7 - dimethoxy - 3,4 - dihydroquinazoline 4 - one, 2 - [N - (N' - methylpiperazino)] - 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one and 2 - amino - 6,7-methylenedioxy - 3,4 - dihydroquinazoline-4 - one. These particular compounds are all highly potent in their antihypertensive effects and they afford a long duration of action as well.

SEE ERRATA SLIP ATTACHED

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Int. Cl.:—C 07 d 51/34, C 07 d 57/00, C 07 d 99/02

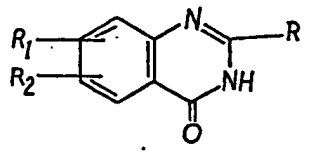
COMPLETE SPECIFICATION

Quinazolone Derivatives

We, CHAS. PFIZER & CO. INC., a Corporation organized under the laws of the State of Delaware, United States of America, of 235 East 42nd Street, New York 17, State of New York, United States of America, do hereby declare the invention, for which we pray that a Patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to certain novel organic nitrogen compounds. More particularly, it is concerned with various new and useful organic nitrogen heterocycles having an amphoteric character and with the salts which such compounds form with pharmacologically acceptable acids and bases.

The amphoteric compounds which are included within the purview of this invention are all selected from the class of 2-amino-3,4-dihydroquinazoline-4-ones of the formulae:



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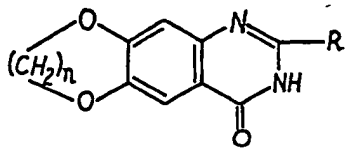


wherein R_1 and R_2 are each hydrogen, fluorine, chlorine, bromine, trifluoromethyl, lower alkyl, lower alkoxy or lower alkylthio, containing from one to four carbon atoms, with at least one of said R_1 and R_2 always being other than hydrogen, n is one or two, and R is amino, N-monoalkylamino, N,N-dialkylamino, N-monohydroxyalkylamino, N,N-di-(hydroxyalkyl)amino, N - monoalkenylamino, N,N-dialkenylamino, N - alkylenyl - N-alkylamino, N - alkyl - N - phenylamino, N - alkyl - N - (*p* - tolyl)amino, N-pyrryl, N-pyrrolidino, N-piperidino, N-homopiperidino, N-morpholino, N-(2,6-dimethylmorpholino), N-piperazino, N-(N'-alkylpiperazino), N-(N'-phenylpiperazino) or N-(1,2,3,4-tetrahydroisoquinolyl) each alkyl and alkenyl group in R containing up to fie carbon atoms. These compounds are all of value in the treatment of hypertension.

Of especial value in this connection and the preferred member compounds of this invention are those of the aforesaid structural formula wherein R_1 and R_2 are each lower alkoxy, and R is N,N-dialkylamino, N,N-dialkenylamino and N-(N'-alkylpiperazino), with the alkyl and alkenyl groups in R containing up to five carbon atoms in each case as previously indicated. Other preferred compounds include those where n is one and R is amino. Typical of the specific members of this series are such compounds as 2 - (N,N - dimethylamino) - 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one, 2 - (N,N - diethylamino) 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one, 2 - (N,N - diallylamino) - 6,7 - dimethoxy - 3,4 - dihydroquinazoline 4 - one, 2 - [N - (N' - methylpiperazino)] - 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one and 2 - amino - 6,7-methylenedioxy - 3,4 - dihydroquinazoline-4 - one. These particular compounds are all highly potent in their antihypertensive effects and they aff rd a long duration of action as well.

SEE ERRATA SLIP ATTACHED

The process employed for preparing the novel compounds of this invention involves treating the corresponding 2 - halo - 3,4 - dihydroquinazoline - 4 - ones with the appropriate amine base, viz., RH where R is as previously defined. In general, it is only necessary that at least an equimolar amount of amine base be employed, but in practice on ordinarily uses an excess of same as this serves to shift the reaction to completion. In addition, the excess amine can also function as a solvent for the reaction. A preferred excess for these purposes would be from about two to about ten moles of amine to one mole of the 2 - halo - 3,4 - dihydroquinazoline - 4-one. If a reaction-inert solvent is employed for the reaction, one would ordinarily use a polar organic solvent such as a lower alkanol like methanol, ethanol and isopropanol, or an aromatic hydrocarbon solvent such as benzene, toluene or xylene. The temperature at which this reaction can be conducted varies within the range of from between 50°C. up to 200°C. for a period of from about one to twelve hours. A preferred reaction temperature and time for this reaction would be about 120—150°C. for about 2—4 hours. In the case where a solvent is used or when the boiling point of the amine is below the desired reaction temperature, a pressure bottle is ordinarily employed as the proper reaction vessel. Upon completion of the reaction, the product is recovered by conventional methods. For instance, evaporation of the reaction mixture to dryness affords a crude solid residual material, which can then be either triturated with water or precipitated from dilute aqueous acid in crystalline form and subsequently recrystallized from any number of appropriate organic solvents, including the N,N-dialkyl lower alkanoamides like dimethylformamide and dimethylacetamide or the lower alkanols such as ethanol and isopropanol.

The starting materials necessary for the reaction procedure of this invention, viz., the 2-halo - 3,4 - dihydroquinazoline - 4 - ones and, preferably, the 2-chloro and 2-bromo compounds, are obtained by treating the corresponding 2,4-dihaloquinazolines with a strong base compound such as an alkali metal hydroxide in an aqueous reaction medium which may also contain an organic solvent as well. A molar excess of base is generally employed, while preferred organic solvents for these purposes include water-miscible inert polar organic solvents like tetrahydrofuran, dioxane and the N,N-dialkyl lower alkanomides, such as dimethylacetamide and dimyethlformamide. The 2,4-dihaloquinazolines, on the other hand, are all obtained by using essentially known methods. For instance, 2,4-dichloro-6,7-dimethoxyquinazoline has been prepared according to the procedure described by F. H. S. Curd et al. in the Journal of the Chemical Society (London), 1948, p. 1759. This procedure is equally applicable to the other starting 2,4-dihaloquinazolines as well, i.e., as regards their method of preparation.

Inasmuch as the 2-amino-3,4-dihydroquinazoline-4-ones of this invention are amphoteric compounds, they are capable of forming a wide variety of salts with various acids and bases, and particularly with the strong acids and bases in view of the nature of the compounds undergoing such a reaction. Some of these salts are pharmaceutically acceptable to begin with, whereas others must first be converted back to the free amphoteric compound and then subsequently converted to the desired salt which is fit for oral human consumption. This is done by simply treating the amphoteric compound with at least a substantially equimolar amount of the chosen acid or base in an aqueous solution or in an organic solvent such as methanol or ethanol. The solid salt is then obtained upon evaporation of the solvent, and this usually occurs in the form of a crystalline residue.

Among the various acids which can be used to prepare the pharmaceutically acceptable acid addition salts of this invention in the manner just described are those which contain pharmacologically acceptable anions such as, for example, hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, acetic acid, lactic acid, citric acid, tartaric acid, oxalic acid, benzoic acid, succinic acid, maleic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid and *p*-toluenesulfonic acid. The bases which can be used include those which form non-toxic salts with these compounds in view of their possession of a pharmacologically acceptable cation. As a result, such bases will generally include the alkali metal and alkaline-earth metal hydroxides like sodium, potassium, calcium and magnesium hydroxide, for example.

As previous indicated, the compounds of the present invention are all readily adapted to therapeutic use as antihypertensive agents in view of their ability to lower the blood pressure of correspondingly agitated subjects. For example, 2 - (N,N - dimethylamino) - 6,7-dimethoxy - 3,4 - dihydroquinazoline - 4 - one has been found to produce a definite antihypertensive response in animals by lowering the blood pressure of hypertensive rats and dogs to a statistically significant degree when orally administered to them. Additionally this particular compound accomplishes this result without causing any unwanted side effects to occur in the subject being so treated. As a matter of fact, no problems of toxicity or any other untoward side effects have ever been encountered with the compounds of this invention when they are administered either orally or parenterally to hypertensive subjects.

In accordance with a method of treatment of the present invention, the herein described

antihypertensives can be administered to an agitated subject via the *oral* or parenteral routes. In general, these compounds are most desirably administered in doses ranging from about 10 mg. up to about 240 mg. per day, although variations will necessarily occur depending upon the weight of the subject being treated and the particular route of administration chosen. However, a dosage level that is in the range of from 0.15 mg. to 4.8 mg per kg. of body weight per day is most desirably employed in order to achieve effective results. Nevertheless, it is to be appreciated that still other variations may also occur in this respect, depending upon the species of animal being treated and its individual response to said medicament, as well as on the particular type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range more be more than adequate, while in other cases still larger dosages may be employed without causing any harmful or deleterious side effects to occur provided that such higher dose levels are first divided into several smaller doses that are to be administered throughout the day.

In connection with the use of the 2 - amino-3,4 - dihydroquinazoline - 4 - one compounds of this invention for the treatment of agitated subjects, it is to be noted that they may be administered either alone or in combination with pharmaceutically acceptable carriers by either of the routes previously indicated, and that such administration can be carried out in both single and multiple dosages. More particularly, the novel compounds of this invention can be administred in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, aqueous suspensions, injectable solutions, elixirs or syrups. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, such oral pharmaceutical compositions can be suitably sweetened and/or flavored by means of various agents of the type commonly employed for just such a purpose. In general, the therapeutically-effective compounds of this invention are present in such dosage forms at concentration levels ranging from 0.5% to 90% by weight of the total composition, i.e., in amounts which are sufficient to provide the desired unit dosage previously indicated.

For purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and dicalcium phosphate may be employed along with various disintegrants such as starch and preferably potato or tapioca starch, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules; preferred materials in this connection would also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the essential active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if so desired, emulsifying and/or suspending agents, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For purposes of parenteral administration, solutions of these particular 2-amino-3,4-dihydroquinazoline-4-ones in sesame or peanut oil or in aqueous-propylene glycol or in N,N-dimethylformamide may be employed as well as sterile aqueous solutions of the corresponding water-soluble, non-toxic salts previously enumerated. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular and intraperitoneal injection purposes. In this connection, the sterile aqueous media employed are readily obtained by standard techniques well-known to those in the art. For instance, distilled water is ordinarily used as the liquid diluent and the final preparation is passed through a suitable bacterial filter, such as a sintered-glass filter or a diatomaceous-earth or unglazed poreclain filter. Preferred filters of this type include the "Berkefeld," the Chamberland and the asbestos disc-metal "Seitz" filter, wherein the fluid is sucked through the filter candle into a sterile container with the aid of a suction pump. The words "Berkefeld" and "Seitz" are Registered Trade Marks. Needless to say, the necessary steps should be taken through the preparation of these injectable solutions to ensure that the final products are obtained in a sterile condition.

This invention is further illustrated by the following preparations and examples.

PREPARATION A.

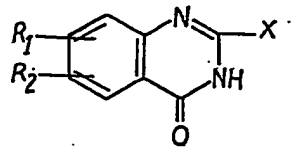
A mixture was prepared consisting essentially of 129 g. of 2,4 - dichloro - 6,7 - dimethoxyquinazoline [prepared according to the method of F. H. S. Curd et al., J. Chem Soc., p. 1759 (1948)] suspended in three liters of 1N aqueous sodium hydroxide and one liter of tetrahydrofuran. This mixture was stirred for approximately two and one-half hours at room temperature before complete solution occurred. Subsequent acidification with glacial acetic acid then afforded a crystalline precipitate,

which was filtered and washed with successive portions of water, benzene and methanol. After drying to constant weight, there were obtained 115 g. (97%) of desired product, viz., 2-chloro - 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one, melting at 267—270° C. (decomp.).

Anal. Calcd. for $C_{10}H_9N_2O_3Cl$: C, 49.90; H, 3.80; N, 11.64; Cl, 14.73.
Found: C, 49.99; H, 3.98; N, 11.56; Cl. 14.43.

PREPARATION B.

The procedure described in Preparation A is repeated to prepare various other 2-halo-3,4-dihydroquinazoline-4-ones of the following formula (where X is halogen), starting from the appropriate 2,4-dihaloquinazoline compounds:

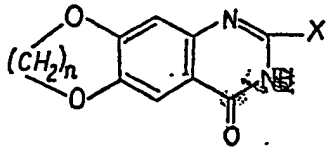


R_1	R_2	X
H	7-Cl	Cl
5-Cl	H	Br
6-Cl	7-Cl	Br
5-F	H	Cl
6-CF_3	H	Br
6-CH_3	H	Cl
5-OCH_3	H	Cl
6-Br	H	Br
H	8-Br	Cl
H	7-CF_3	Br
H	7-(n-C_3H_7	Br
H	8-OC_2H_5	Cl
6-CH_3	7-CH_3	Cl
H	8-F	Cl
5-SCH_3	H	Br
H	8-OCH_3	Cl
6-F	H	Br
6-CF_3	7-CF_3	Cl
5-OC_2H5	H	Br
6-(n-C_3H_7)	7-(n-C_3H_7)	Br
H	8-Cl	Cl

R_1	R_2	X
H	7-SC_2H_5	Cl
H	7-OCH_3	Cl
5-Cl	8-C_3H_7	Br
H	7-Br	Cl
5-OC_2H_5	H	Cl
6-OCH_3	7-OCH_3	Cl
6-OCH_3	7-OCH_3	Br
H	8-SC_3H_7	Br
6-OCH_3	7-OCH_3	Br
H	7-(n-C_4H_9)	Cl
5-OC_3H_7	7-Cl	Br
6-Br	7-Br	Cl
6-SCH_3	7-SCH_3	Cl
5-SC_3H_7	H	Cl
6-OC_2H_5	7-OC_2H_5	Cl
6-F	7-OCH_3	Cl
H	8-CF_3	Br
6-OC_3H_7	7-OC_3H_7	Cl

PREPARATION C.

The procedure described in Preparation A is repeated to prepare various other 2-halo-3,4-dihydroquinazoline-4-ones of the following formula (where X is halogen), starting from the appropriate 2,4-dihaloquinazoline compounds:



n	X	Compound Name
1	Cl	2-chloro-6,7-methylenedioxy-3,4-dihydroquinazoline-4-one
2	Br	2-bromo-6,7-ethylenedioxy-3,4-dihydroquinazoline-4-one
2	Cl	2-chloro-6,7-ethylenedioxy-3,4-dihydroquinazoline-4-one
1	Br	2-bromo-6,7-methylenedioxy-3,4-dihydroquinazoline-4-one

EXAMPLE I.

A mixture of 4.8 g. (0.03 mole) of 2-chloro-6,7 - dimethoxy - 3,4 - dihydroquinazoline-4 - one and 10 ml. of diethylamine (7.1 g., 0.0973 mole) in 50 ml. of ethanol was placed in a pressure bottle and shaken at 130° C. for three hours. The reaction mixture was then cooled to room temperature, the solvent removed by means of evaporation under reduced pressure and the residual material triturated with water. The solid product so obtain was then collected by means of suction filtration and recrystallized once from ethyl alcohol to afford a 70% yield of 2-(N,N-diethylamino) - 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one, m.p. 215—217° C.

Anal. Calcd. for $C_{14}H_{19}N_3O_3$: C, 60.63; H, 6.91; N, 15.15.
Found: C, 60.39; H, 6.67; N, 15.36.

EXAMPLE II.

A mixture of 4.89 g. (0.03 mole) of 2-chloro-6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4-one and 4.5 g (0.10 mole) of dimethylamine in 50 ml. of ethanol is treated in exactly the same manner as described before in the reaction procedure for Example I. In this particular case, it was found that 2 - (N,N - dimethylamino) - 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one was the product obtained (m.p. 246—248° C.).

Anal. Calcd. for $C_{12}H_{15}N_3O_3$: C, 57.82; H, 6.07; N, 16.86.
Found: C, 57.52; H, 5.92; N, 16.68.

EXAMPLE III.

The procedure described in Example I was followed except that diallylamine (9.7 g., 0.10 mole) was the organic base employed instead of diethylamine. In this particular case, the product obtained was 2 - (N,N - diallylamino) - 6,7 - dimethoxy - 3,4 - dihydroquinazoline -4 - one, m.p. 190—191° C.

Anal. Calcd. for $C_{16}H_{19}N_3O_3$: C, 63.77; H, 6.36; N, 13.95.
Found: C, 63.58; H, 6.10; N, 13.77.

EXAMPLE IV.

The procedure described in Example I was followed except that N-methyl-piperazine (10 g., 0.10 mole) was the organic base employed instead of diethylamine. In this particular case, the product obtained was 2 - [N - (N'-methylpiperazine)] - 6,7 - dimethoxy - 3,4-dihydroquinazoline - 4 - one, m.p. 250—252° C.

Anal. Calcd. for $C_{15}H_{20}N_4O_3$: C, 59.19; H, 6.62; N, 18.41.
Found: C, 59.47; H, 6.60; N, 18.29.

EXAMPLE V.

The procedure described in Example I was followed to prepare the compounds listed below, except that the appropriate amine base substituted as reagent in place of diethylamine on the same molar basis as before:

2 - Amino - 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one, m.p. 317—319° C.

2 - (N - monomethylamino) - 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one, m.p. 294—296° C.

2 - (N - monoethylamino) - 6,7 - dimethoxy-3,4 - dihydroquinazoline - 4 - one, m.p. 262—264° C.

2 - [N - mono(n - propyl)amino] 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one, m.p. 216—218° C.

2 - (N - monoisopropylamino) - 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one, m.p. 242—244° C.

2 - [N - mono(n - butyl)amino] - 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one, m.p. 184—186° C.

2 - (N - monoisoamylamino) - 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one, m.p. 177—179° C.

2 - [N,N - di(n - propyl)amino] 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one, m.p. 197—200° C.

2 - [N,N - di (n - butyl)amino] - 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one, m.p. 167—169° C.

2 - [N,N - di(n - amyl) amino] - 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one, m.p. 145—148° C.

2 - (N - monoallylamino) - 6,7 - dimethoxy-3,4 - dihydroquinazoline - 4 - one, m.p. 221—227° C.

2 - [N - mono(β - hydroxyethyl)amino] - 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4-one, m.p. 239—240° C.

2 - [N - mono(α - hydroxymethyl) - n-propyl)amino] - 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one, m.p. 234—236° C.

2 - [N,N - di(β - hydroxyethyl)amino] - 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one, m.p. 189—193° C.

2 - (N - pyrrolidino) - 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one, m.p. 246—249° C.

2 - (N - piperidino) - 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one, m.p. 263—265° C.

2 - (N - homopiperidino) - 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one, m.p. 253—555° C.

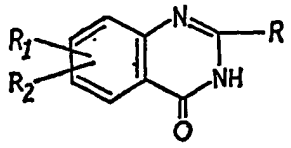
2 - (N - morpholino) - 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one, m.p. 274—276° C.

2 - [N - (2,6 - dimethylmorpholino)] - 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one, m.p. 316—318° C.

2 - [N - (N' - phenylpiperazino)] - 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one, m.p. 269—271° C.

EXAMPLE VI.

The procedure of Example I is again employed to prepare the following compounds, which are listed below in the table of this example, starting from the appropriate 2-halo - 3,4 - dihydroquinazoline - 4 - ones (of Preparations A and B) and the corresponding amines:

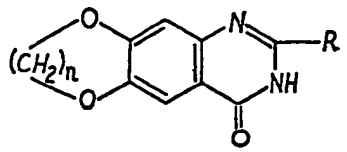


R_1	R_2	R
H	7-Cl	NH_2
5-Cl	H	$NH(n\text{-}C_5H_{11})$
6-Cl	7-Cl	$NH(iso\text{-}C_3H_7)$
5-F	H	$N(n\text{-}C_5H_{11})_2$
6-CF_3	H	$NH[(CH_2)_5OH]$
6-CH_3	H	$N[(CH_2)_3OH]_2$
5-OCH_3	H	$NH(C_3H_7CH{=}CH_2)$
6-Br	H	morpholino
H	8-Br	$N(CH_2CH{=}CHC_2H_5)_2$
H	7-CF_3	$N(CH_3)C_6H_5$
H	7-$(n\text{-}C_3H_7)$	$N(CH_3)C_6H_4{-}CH_3(p)$
H	8-OC_2H_5	pyrryl
6-CH_3	7-CH_3	$N(C_2H_5)_2$
H	8-F	pyrrolidino
5-SCH_3	H	NH_2
H	8-OCH_3	piperidino
6-F	H	$N(CH_2)_6$
6-CF_3	7-CF_3	$NHCH_2CH_2OH$
5-OC_2H_5	H	morpholino
6-$(n\text{-}C_3H_7)$	7-$(n\text{-}C_3H_7)$	$N(n\text{-}C_3H_7)C_6H_5$

R_1	R_2	R
H	8-Cl	piperazino
H	7-SC_2H_5	N-(n-amyl) piperazino
H	7-OCH_3	N-phenylpiperazino
5-Cl	8-OC_3H_7	NH_2
H	7-Br	$NHCH_3$
5-OC_2H_5	H	$N(n\text{-}C_5H_{11})CH{=}CH_2$
6-OCH_3	7-OCH_3	$N(CH_3)$allyl
6-OCH_3	7-OCH_3	N-hydroxyethylpiperazino
H	8-SC_3H_7	N-hydroxyamylpiperazino
6-OCH_3	7-OCH_3	1, 2, 3, 4-tetrahydroisoquinolyl
H	7-(n-C_4H_9)	$N(C_2H_5)_2$
5-OC_3H_7	7-Cl	NHC_2H_5
6-Br	7-Br	$N(CH_3)_2$
6-SCH_3	7-SCH_3	N-methylpiperazino
5-SC_3H_7	H	$NHCH_2CH{=}CH_2$
6-OC_2H_5	7-OC_2H_5	morpholino
6-F	7-OCH_3	$N(C_2H_5)C_6H_4$—$CH_3(p)$
H	8-CF_3	pyrryl
6-OC_3H_7	7-OC_3H_7	$N(CH_2CH{=}CH_2)_2$

EXAMPLE VII.

The procedure of Example I is again employed to prepare the following compounds, which are listed below in the table of this example, starting from the appropriate 2-halo-3,4-dihydroquinazoline-4-one (of Preparation C) and the corresponding amines:



n	R	n	R
1	NH_2	1	morpholino
2	NH(n-C_5H_{11}	2	2,6-dimethylmorpholino
1	$N(C_2H_5)_2$	1	piperazino
2	$NHCH_2CH_2OH$	2	N-(n-amyl) piperazino
1	$N[(CH_2)_3OH]_2$	1	N-phenylpiperazino
1	$NHCH_2$-CH=CH_2	2	1,2,3,4-tetrahydroisoquinolinyl
2	$N(CH_2CH=CHC_2H_5)_2$	1	$N(CH_2)_6$
1	$N(CH_3)CH_2CH=CH_2$	2	$N(CH_3)_2$ (m.p. 290—292°C.)
2	N(n-C_5H_{11})C_6H_5	1	N(n-C_5H_{11})$_2$
1	$N(CH_3)C_6H_4$—CH_3(*p*)	2	$NH[(CH_2)_5OH]$
2	pyrryl	1	$N[(CH_2)_5OH]_2$
2	NH_2	2	$N(CH_2CH=CHC_2H_5)_2$
1	pyrrolidino	1	N(n-C_5H_{11})$CH_2CH=CH_2$
2	piperidino	2	N(n-C_5H_{11})C_6H_4—CH_3(*p*)

EXAMPLE VIII.

The hydrochloride salt of 2 - (N,N - diethylamino) - 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one was prepared by dissolving the compound in an aqueous solution containing an equivalent amount in moles of hydrochloric acid. Actually, aqueous 1*N* HCl was used for these purposes. Upon completion of this step, the resultant solution was then evaporated to dryness while under reduced pressure to afford the desired salt in the form of a crystalline residue. In this manner, there was obtained 2 - (N,N - diethylamino) - 6,7-dimethoxy - 3,4 - dihydroquinazoline - 4 - one hydrochloride, m.p. 250—251° C.

Anal. Calcd. for $C_{14}H_{19}N_3O_3$ HCl: C, 53.59; H, 6.42; N, 13.37.
Found: C, 53.73; H, 6.54; N, 13.49.

EXAMPLE IX.

The procedure described in Example VIII is repeated to prepare other hydrochlorides, which are listed below in the table together with their melting points. In each case, elementary analysis for carbon, hydrogen, nitrogen and chlorine agrees with the calculated values.

2 - Amine - 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one hydrochloride, m.p. 277—279° C.

2 - (N - monomethylamino) - 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one

hydrochloride, m.p. 334—336° C.

2 - (N - monoethylamino) - 6,7 - dimethoxy-3,4 - dihydroquinazoline - 4 - one hydrochloride, m.p. 293—294° C.

2 - [N - mono(n - propyl)amino - 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one hydrochloride, m.p. 299—300° C.

2 - [N - mono(n - butyl)amino - 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one hydrochloride, m.p. 294—296° C.

2 - (N,N - dimethylamino) - 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one hydrochloride, m.p. 279—282° C.

2 - [N,N - di(n - propyl)amino] - 6,7-dimethoxy - 3,4 - dihydroquinazoline - 4 - one hydrochloride, m.p. 237—239° C.

2 - (N - monoallylamino) - 6,7 - dimethoxy-3,4 - dihydroquinazoline - 4 - one hydrochloride, m.p. 293—294° C.

2 - (N,N - diallylamino) - 6,7 - dimethoxy-3,4 - dihydroquinazoline - 4 - one hydrochloride, m.p. 233—235° C.

2 - (N - pyrrolidino) - 6,7 - dimethoxy-3,4 - dihydroquinazoline - 4 - one hydrochloride, m.p. 269—271° C.

2 - (N - piperidino) - 6,7 - dimethoxy - 3,4-dihydroquinazoline - 4 - one hydrochloride, m.p. 256—257° C.

2 - (N - homopiperidino) - 6,7 - dimethoxy-3,4 - dihydroquinazoline - 4 - one hydrochloride, m.p. 244—245° C.

2 - (N - morpholino) - 6,7 - dimethoxy-3,4 - dihydroquinazoline - 4 - one hydrochloride, m.p. 261—265° C.

2 - [N - (2,6 - dimethylmorpholino)] - 6,7-dimethoxy - 3,4 - dihydroquinazoline - 4 - one hydrochloride, m.p. 277—281° C.

2 - [N - (N' - methylpiperazino)] - 6,7-dimethoxy - 3,4 - dihydroquinazoline - 4 - one hydrochloride, m.p. 242—245° C.

2 - [N - (N' - phenylpiperazino)] - 6,7-dimethoxy - 3,4 - dihydroquinazoline - 4 - one hydrochloride, m.p. 276—277° C.

EXAMPLE X.

The other acid addition salts of the novel 2 - amino - 3,4 - dihydroquinazoline - 4-ones of this invention like 2 - (N,N - diethylamino) - 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one hydrobromide are prepared by the same general procedure described in Example VIII, except that in the case of the hydrobromide, hydriodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, methanesulfonate, ethanesulfonate, benzenesulfonate and *p*-toluenesulfonate salts, the corresponding appropriate organic or mineral acid is employed in place of hydrochloric acid, with comparable results being obtained in each instance.

In like manner, ethanol can be substituted for water in this very same procedure with comparable results also being obtained. For instance, when the respective acid and 2-(N,N - diethylamino) - 6,7 - dimethoxy - 3,4-dihydroquinazoline - 4 - one are both separately dissolved in ethanol and the two solutions are then mixed, followed by the addition of diethyl ether to the resulting reaction mixture, there is obtained the desired acid addition salt in the form of a crystalline precipitate from said solution. This method has also been used to prepare the corresponding acetate, lactate, citrate or acid citrate, tartrate or bitartrate, oxalate, benzoate, succinate and maleate salts of the 2 - amino - 3,4 - dihydroquinazoline-4 - one compounds of this invention as well.

EXAMPLE XI.

The sodium salt of 2 - (N,N - diethylamino)6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one is prepared by dissolving the compound in water, i.e., in an aqueous solution containing a sufficient amount of sodium hydroxide to be equimolar with respect to the amphoteric organic base. Upon freeze-drying of the mixture, the desired alkali metal salt is obtained.

EXAMPLE XII.

The potassium salt of N - (N,N - dimethylamino) - 6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4 - one is prepared by dissolving the compound in an aqueous solution containing an equivalent amount in moles of potassium hydroxide. The resultant solution is then concentrated under reduced pressure to obtain the desired potassium salt.

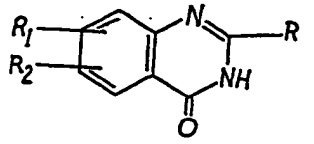
EXAMPLE XIII.

Other alkali metal and alkaline-earth metal salts of the novel 2 - amino - 3,4 - dihydroquinazoline - 4 - ones of this invention are prepared according to the general procedure of the preceding two examples by merely substituting the appropriate amphoteric organic base and alkali or alkaline-earth metal reagent, as the case may be, to obtain the desired results. For instance, 2 - (N,N - diallylamino)-6,7 - dimethoyl - 3,4 - dihydroquinazoline-4 - one and calcium hydroxide react in this manner to afford the corresponding calcium salt.

In like manner, the corresponding lithium, sodium, potassium, calcium, barium, strontium and magnesium salts of all these compounds are also obtained.

WHAT WE CLAIM IS:—

1. A process for preparing a 2-amino-3,4-dihydroquinazoline-4-one of the formula



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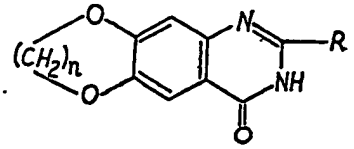


wherein R_1 and R_2 are each hydrogen, fluorine, chlorine, bromine, trifluoromethyl, lower alkyl, lower alkoxy or lower alkylthio, containing from one to four carbon atoms with at least one of said R_1 and R_2 always being other than hydrogen, n is one or two, and R is amino, N-monoalkylamino, N,N-dialkylamino, N-monohydroxyalkylamino, N,N - di(hydroxyalkyl)amino, N-monoalkenylamino, N,N-dialkenylamino, N-alkenyl-N-alkylamino, N-alkyl-N-phenylamino, N-alkyl-N-(*p*-tolyl)amino, N-pyrryl, N-pyrrolidino, N-piperidino, N-homopiperidino, N-morpholino, N-(2,6-dimethylmorpholino), N-piperazino, N-(N'-alkylpiperazino), N-(N'-phenylpiperazino) or N-(1,2,3,4-tetrahydroisoquinolyl), each alkyl and alkenyl group in R containing up to five carbon atoms, which comprises reacting the 4-one with an amine base of the formula RH where R is as defined above.

2. A process according to claim 1 wherein at least an equimolar amount of the amine base is employed.

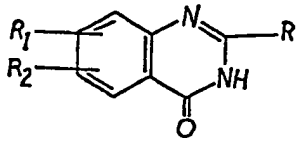
3. A process according to claim 1 or 2 wherein the reaction is conducted at a temperature between 50° and 200°C.

4. A process according to any of the preceding claims wherein the product is converted to a salt by treatment with a suitable non-toxic acid or base.

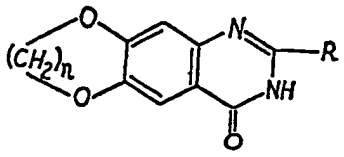
5. A process for preparing a 2-amino-3,4-dihydroquinazoline-4-one or a salt thereof substantially as described herein with particular reference to the Examples herein.

6. A 2-amino-3,4-dihydroquinazoline-4-one or a salt thereof whenever prepared by a process according to any of the preceding claims.

7. 2-Amino-3,4-dihydroquazoline-4-ones of the formulae



or



and salts thereof with pharmacologically acceptable acids and bases; wherein R_1 and R_2 are each hydrogen, fluorine, chlorine, bromine, trifluoromethyl, lower alkyl, lower alkoxy or lower alkylthio, containing from one to four carbon atoms with at least one of said R_1 and R_2 always being other than hydrogen; n is ne or two, and R is amino, N-monoalkylamino, N,N-dialkylamino, N-monohydroxyalkylamino, N,N-di(hydroxyalkyl)-amino, N-monoalkenylamino, N,N-dialkenylamino, N-alkenyl-N-alkylamino, N-alkyl-N-phenylamino, N-alkyl-N-(*p*-tolyl)amino, N-pyrryl, N-pyrrolidino, N-piperidino, N-homopiperidino, N-morpholino, N-(2,6-dimethylmorpholino), N-piperazino, N-(N'-alkylpiperazino), N-(N'-hydroxyalkyl)piperazino, N-(N'-phenylpiperazino) or N-(1,2,3,4-tetrahydroisoquinolyl), each alkyl and alkenyl group in R containing up to five carbon atoms.

8. A compound according to claim 7 wherein R_1 and R_2 are each lower alkoxy, and R is N,N-dialkylamino or dialkenylamino and salts thereof with pharmacologically acceptable acids and bases.

9. A compound according to claim 7 or 8 wherein R_1 and R_2 are each lower alkoxy, and R is N-(N'-alkylpiperazino) and salts thereof with pharmacologically acceptable acids and bases.

10. A compound according to claim 7 wherein n is one, and R is amino, or N,N-dialkylamino and salts thereof with pharmacologically acceptable acids and bases.

11. 2-(N,N-Diethylamino)-6,7-dimethoxy-3,4-dihydroquinazoline-4-one and salts thereof with pharmacologically acceptable acids and bases.

12. 2-(N,N-Diallylamino)-6,7-dimethoxy-3,4-dihydroquinazoline-4-one and salts thereof with pharmacologically acceptable acids and bases.

13. 2 - [N - (N' - Methylpiperazino)]-6,7 - dimethoxy - 3,4 - dihydroquinazoline - 4-one and salts thereof with pharmacologically acceptable acids and bases.

14. 2 - (N,N - Dimethylamino) - 6,7-dimethoxy - 3,4 - dihydroquinazoline - 4-one and salts thereof with pharmacologically acceptable acids and bases.

15. 2 - (N - Monoisopropylamino) - 6,7-dimethoxy - 3,4 - dihydroquinazoline - 4-one and salts thereof with pharmacologically acceptable acids and bases.

16. 2 - Amino - 6,7 - methylenedioxy-3,4 - dihydroquinazoline - 4 - one and salts thereof with pharmacologically acceptable acids and bases.

17. 2 - (N,N - Dimethylamino) - 6,7-ethylenedioxy - 3,4 - dihydroquinazoline - 4-one and salts thereof with pharmcologically acceptable acids and bases.

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